REMARKS

I. Pending Claims

Claims 1-9, 11-17, 19-20, 24-28 and 46 are currently pending. Of these, claims 1, 3, 4, and 9 are currently amended, and claims 1, 2, 8, 13-17, 19-20, and 24-28 are withdrawn from consideration. Claims 10, 18, 21-23, and 29-45 have been canceled. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

II. Support for the Amendments

Claims 3, 4, and 9 have been amended to incorporate all limitations of non-elected claims 1 and 2, from which they had depended. Claim 3 has been amended to recite in part b), a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:2, said polypeptide having thioredoxin activity, and in part c), a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:2, said fragment having thioredoxin activity. Support for this amendment may be found in the Specification at pp. 1-2 wherein it is set forth that SEQ ID NO:2 is a substantially purified polypeptide referred to as "TRXP-2," having the ability to catalyze the formation of disulfide bonds and regulate the redox environment in cells to enable the necessary thiol:disulfide exchanges. Also, the Specification, at p. 42, Example X, describes an assay to measure thioredoxin reductase activity.

III. Restriction Requirement/Election

It is noted that election, with traverse, has been acknowledged by the Examiner of the claims of Group II (encompassing claims 3-7, 9, 11, 12, and 46), drawn to polynucleotides, a vector, a host cell, and methods of expression., with respect to SEQ ID NO:4. Applicants also acknowledge that the Examiner has further stated that "upon allowance of a produce claim, method claims comparable in scope to the allowed product claim will be rejoined" (Office Action of September 24, 2003; p. 2).

IV. Claim objections

The Examiner has objected to claims 3, 4, and 9 as "depend[ing] on unelected claims, claims 1 and 2" (Office Action of September 24, 2003; p. 10). Applicants have amended claim 3 to incorporate all limitations of non-elected claim 1 from which it had depended. Further, Applicants have amended claims 4 and 9 to refer to the polypeptides recited in claim 3.

V. Priority

The Examiner has stated that since the claimed invention in Application Serial No. 09/954,846, which is a divisional of application 09/107,248, does not appear to have patentable utility, the claimed subject matter is not entitled to the priority filing date of 09/107,248, June 30, 1998 (Office Action of September 24, 2003; pp. 2-3). Further, the Examiner has rejected claims 3, 4, 6, 7, 9, 11, and 12 under 35 U.S.C. § 102(b) as being anticipated by Kato et al. (WO200005376-A2, February 3, 2000). The priority application (Tang 09//107,248) has a priority date of June 30, 1998. The priority application has substantially the same disclosure as the instant application, and any arguments in rebuttal of the utility rejection in the instant application will also establish the validity of the claim to priority. Therefore, Applicants find no need to substantively address the prior art rejection until the utility issue has been settled; other than by claiming the priority date of June 30, 1998 as valid, and stating therefore that the Kato et al. reference is not prior art.

VI. Utility Claim Rejection Under 35 U.S.C. §§ 101

Claims 3-7, 9, 11, 12 and 46 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that the claimed invention is not "supported by either a specific and substantial asserted utility or a well-established utility" (Office Action of September 24; 2003, p. 3).

The rejection of claims 3-7, 9, 11, 12, and 46 is improper, as the inventions of those claims have a patentable utility as set forth in the instant Specification, and/or a utility well known to one of ordinary skill in the art.

Applicants' invention is directed, *inter alia*, to a polynucleotide encoding a polypeptide ("TRXP-2") having a thioredoxin family motif. The polynucleotide at issue is a sequence corresponding to a gene that is expressed in human gastrointestinal, hematopoietic/immune and urologic tissues (see Table 3). Both the polynucleotide and the polypeptide have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of "TRXP-2", for toxicology testing, and for drug discovery (see the Specification at, e.g., page 34-36).

Applicants respectfully submit that evidence is presented in the Specification in support of the assertion that TRXP-1 and TRXP-2 are members of the thioredoxin family of proteins. The Specification, for example, at p. 13, lines 11-13 and again at lines 27-28 discloses a thioredoxin family active site signature present in both proteins that is common to all family members. The active site pair of cysteine residues necessary for thiol reduction is found within this signature at amino acid residues C66 and C69 of TRXP-1 (SEQ ID NO:1; Figure 1A).

Applicants have also disclosed that TRXP-2 is predominately expressed in tissues involved in cell proliferative disorders, such as cancer, and inflammatory disorders by Northern Analysis (Specification at p. 13, lines 25-27), a method which is described in detail at page 37, Example IV, and may therefore be useful as markers for these disorders (p. 28, lines 35-37). Details of that Northern analysis are presented in attached Table 1 and demonstrating that various tumor tissues and inflammatory conditions are found to overexpress TRXP (e.g. abundance greater than 1). In addition, various tumor tissues are matched with macroscopically normal tissue from the same donor, in which TRXP is found at a distinctly lower level (i.e., BRSTTUT03 vs BRSTNOT05), or is undetectable (i.e., KIDNTUT16 vs KIDNNOT26). Thus, Applicants' assertion that TRXP may be a marker for these conditions is both credible and supported by evidence.

The fact that the claimed polynucleotide is a member of the thioredoxin protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide, as well as the polynucleotide encoding the polypeptide, also

have patentable utility, regardless of the actual function of the claimed polypeptide. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this Response the Declaration of Dr. Tod Bedilion (hereinafter "the Bedilion Declaration") describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on June 30, 1998] that cDNA microarrays that contained the SEQ ID NO:2-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer/cell proliferation and inflammation/trauma for such purposes as evaluating their efficacy and toxicity (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

The Examiner states that claims 3-7, 9, 11, 12, and 46 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility (Office Action of September 24, 2003; p. 4).

Yet, the Office Action fails to acknowledge, let alone address, the Tang '248 disclosure that cDNA microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Tang '846 application at p. 34, lines 8-10).

A. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

B. Use of the Claimed Polynucleotides for Diagnosis of Conditions and Disorders Characterized by Expression of TRXP, for Toxicology Testing, and for Drug Discovery are Sufficient Utilities Under 35 U.S.C. §§ 101 and 112, First Paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's Specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '248 application on June 30, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide

in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "Tang '248 Specification would have led a person skilled in the art on June 30, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of (a) cancer/cell proliferation and inflammation/trauma (Table 3) to conclude that a cDNA microarray that contained the SEQ ID NO:2-encoding polynucleotides would be a highly useful tool, and (b) to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:2-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would have appreciated on June 30, 1998 that a cDNA microarray that contained the SEQ ID NO:2-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer/cell proliferation and inflammation/trauma for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-June 30, 1998 publications showing the state of the art on June 30, 1998 (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on June 30, 1998 (and for several years prior to June 30, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Bandman '388 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

development of the drug" and how the teachings of the Tang '248 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Tang '248 application at the time it was filed "would have wanted their cDNA microarray to have a SEQ ID NO:2-encoding polynucleotide probe because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 30, 1998"(Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Tang '248 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pp. 32-35 of the Tang '846 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., <u>they are useful in analyzing compounds</u>)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-June 30, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression

monitoring applications at the time the Tang '248 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Tang '248 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
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> * * *
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> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a

> xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination (*emphasis added*).

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, (1999) Xenobiotica 29:655-691 (Reference No. 1).

In another pre-June 30, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) 94 Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (emphasis added) (Reference No. 2).

2. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999) (Reference No. 3); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology - - potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No. 4).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxTRXPe proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, (1999) (Reference No. 5). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 6), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

3. The uncontested fact that the claimed polynucleotide encodes for a protein in the thioredoxin protein family also demonstrates utility

Because there is a substantial likelihood that the claimed polynucleotide encodes TRXP-2, which is a member of the family of polypeptides known as thioredoxin proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polynucleotide has the sequence shown as SEQ ID NO:4 in the patent application and referred to as TRXP in that application. Applicants have demonstrated by more than reasonable probability that SEQ ID NO:4 encodes a protein that is a member of the thioredoxin protein family. Applicants respectfully submit that evidence is presented in the Specification in support of the assertion that TRXP-1 and TRXP-2 are members of the thioredoxin family of proteins. The Specification, for example, at p. 13, lines 11-13 and again at lines 27-28 discloses a thioredoxin family active site signature present in both proteins that is common to all family members. The active site pair of cysteine residues necessary for thiol reduction is found within this signature at amino acid residues C66 and C69 of TRXP-1 (SEQ ID NO:1; Figure 1A).

The Patent Examiner does not dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept the Applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the thioredoxin protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the thioredoxin protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the thioredoxin protein family, useful.

4. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12

USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra.*

C. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities (Office Action at p. 4). The Examiner is incorrect both as a matter of law and as a matter of fact.

1. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological role of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the thioredoxin protein family, the Examiner refused to impute the utility of the members of the thioredoxin protein family to TRXP. In the Office Action, the Patent Examiner takes the position that, unless Applicants can identify which particular biological function within the class of thioredoxin proteins is possessed by TRXP, utility cannot be imputed. To demonstrate utility by membership in the class of thioredoxin proteins, the Examiner would require that all thioredoxin proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did

not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[2]

The Examiner addresses TRXP as if the general class in which it is included is not the thioredoxin protein family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the thioredoxin protein family does not. The thioredoxin protein family is sufficiently specific to rule out any reasonable possibility that TRXP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the thioredoxin protein class of redox proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the TRXP encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide is also useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the thioredoxin protein family would meet it. It is undisputed that known members of the redox protein family are regulators of enzymes by redox control. A person of ordinary skill in the art need not know any more about how the claimed invention participates in redox control to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given thioredoxin protein regulates enzymes by redox control. The Examiner then goes on to assume that the only use for TRXP absent knowledge as to how the thioredoxin protein actually works is further study of TRXP itself (Office Action of September 24, 2003; p. 4).

Not so. As demonstrated by Applicants, knowledge that TRXP is a thioredoxin protein is more than sufficient to make it useful for the diagnosis and treatment of cancer/cell proliferation and inflammation/trauma and the immune response (Specification at p. 13, lines 25-27). The Examiner must

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[2]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

3. Because the uses of polynucleotides encoding TRXP-2 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility

The PTO rejection of the claims is tantamount to a rejection based on the sequence being only a research tool. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and

find what use they do have as medicines"). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility". These include the use of the claimed polynucleotides in disease diagnosis, expression profiling, drug discovery, and chromosomal mapping (Specification at, e.g., p. 32-36).

D. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide

> whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p. 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the Specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the Specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being

homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of non-useful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

E. To the Extent the Rejection of the Claimed Invention Under 35 U.S.C. § 112, First Paragraph, is Based on an Improper Rejection for Lack of Utility Under 35 U.S.C. § 101, it Must be Reversed

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

CONCLUSION

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly

distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[3] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

VII. Written Description Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 3, 6, 7, 9, 11, and 12 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Note that claim 3 has been amended to recite in part b), a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:2, said polypeptide having thioredoxin activity, and in part c), a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:2, said fragment having thioredoxin activity. Support for this amendment may be found in the Specification at pp. 1-2 wherein it is set forth that SEQ ID NO:2 is a substantially purified polypeptide referred to as "TRXP-2," having the ability to catalyze the formation of disulfide bonds and regulate the redox environment in cells to enable the necessary

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[3]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

thiol:disulfide exchanges. Also, the Specification, at p. 42, Example X, describes an assay to measure thioredoxin reductase activity. Therefore, it would not constitute undue experimentation for one skilled in the art to determine which polynucleotides having at least 90% identity to the claimed sequences would also retain thioredoxin activity. Applicants, therefore, respectfully request withdrawal of the rejection of claims 3, 6, 7, 9, 11, and 12 under 35 U.S.C. § 112, first paragraph.

Furthermore, the requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (footnotes omitted).

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:4 is specifically disclosed in the application (see, for example, and p. 3 of the Sequence Listing). Variants of SEQ ID NO:4 are disclosed in the Specification, for example, on p. 13, line 35 through p. 14, line 9 of the Specification. Incyte clones in which the nucleic acids encoding the human TRXP-2 were first identified and libraries from which those clones were isolated are disclosed, for example, on p. 13, lines 13-18. Chemical and structural features of TRXP-2 are disclosed, for

example, on p. 13, lines 19-27. Given SEQ ID NO:4, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:4 having 90% sequence identity to SEQ ID NO:4. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Present Claims Specifically Define the Claimed Genus Through the Recitation of Chemical Structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claim 3, as amended, recites chemical structure to define the claimed genus:

3. An isolated polynucleotide encoding an isolated polypeptide selected from the group consisting of:
    a) a polypeptide comprising an amino acid sequence of SEQ ID NO:2,
    b) a polypeptide comprising a naturally occurring amino acid sequence at least 90%identical to an amino acid sequence of SEQ ID NO:2, said polypeptide having thioredoxin activity,
    c) a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:2, said fragment having thioredoxin activity, and
    d) an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:2.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The Present Claims do not Define a Genus Which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope. In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078 (Reference No. 7)). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case

for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to TRXP proteins related to the amino acid sequence of SEQ ID NO:2. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as TRXP proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:2. The "variant language" of the present claims recites, for example, polynucleotides encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:2 ..." (note that SEQ ID NO:2 has 258 amino acid residues). This variation is far less than that of all potential TRXP proteins related to SEQ ID NO:2, i.e., those TRXP proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:2.

C. The State of the Art at the Time of the Present Invention is Further Advanced than at the Time of the *Lilly* and *Fiers* Applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 30, 1998. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present

inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

VIII. Indefiniteness Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 11 and 46 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has stated that claim 11 (and claim 46, dependent therefrom) is indefinite in the recitation of "an RNA equivalent" (Office Action of September 24, 2003; p. 9). Applicants respectfully disagree and traverse the rejection.

Applicants submit that "an RNA equivalent" in reference to a DNA molecule, is composed of the same linear sequence of nucleotides as the reference DNA molecule with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

A. The Claims Must be Examined on the Basis of Whether One Having Ordinary Skill in the Art Would be Able to Determine the Scope of the Claim

One of skill in the art would readily be able to determine the meaning of the term "an RNA equivalent." The M.P.E.P. provides guidelines to Examiners for rejections under 35 U.S.C. § 112, second paragraph as follows:

> ...a full explanation of the deficiency of the claims should be supplied. Whenever possible, identify the particular term(s) or limitation(s) which render the claim(s) indefinite and state why such term or limitation renders the claim indefinite. If the scope of the claimed subject matter can be determined by one having ordinary skill in the art, a rejection using this form paragraph would not be appropriate (M.P.E.P. § 706.03(d)).

Therefore, claims must be examined on the basis of whether one having ordinary skill in the art would be able to determine the scope of the claim and, if a rejection is made, reasons must be provided why the claim is indefinite. Applicants submit that the Examiner has not provided any reasons or evidence why the cited phrase is indefinite and/or why one having ordinary skill in the art could not determine the scope of the claim. For this reason alone, the rejection is improper and should be withdrawn.

B. The Term "an RNA equivalent" is Well-Understood in the Art

Applicants submit that "an RNA equivalent" has the plain meaning of the words, and that the skilled artisan would understand that "an RNA equivalent" in reference to a DNA molecule, is composed of the same linear sequence of nucleotides as the reference DNA molecule with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

As a general rule, claim language carries the ordinary and accustomed meaning of the words in their normal usage in the field of invention (Toro Co. v. White Consol. Indus., 199 F.3d 1295, 53 USPQ2d 1065, 1067 Fed. Cir. 1999). The dictionary defines "RNA" as "any of various nucleic acids that contain ribose and uracil as structural components and are associated with the control of cellular

chemical activities", and "equivalent" as "corresponding or virtually identical especially in effect or function" and "having the same chemical combining capacity, i.e., *equivalent* quantities of two elements" (Reference No. 8; Merriam-Webster's Collegiate Dictionary; Merriam-Webster OnLine: http://www.m-w.com).

Applicants also call the Examiner's attention to M.P.E.P § 2111.01, which states that "[p]lain meaning refers to the meaning given to the term by those of ordinary skill in the art."
Thus, one of skill in the art would understand the meaning of the term "an RNA equivalent" within the context of the claims.

C. The Specification Contains Adequate Support for the Meaning of the Term, "an RNA equivalent"

There is adequate definition of the term "an RNA equivalent" in the Specification. An inventor may act as his own lexicographer and use the Specification to supply new meanings for terms implicitly or explicitly (Markman v. Westview Instruments, Inc., 52 F.3d 967, 979-80, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995) en banc, aff'd 517 U.S. 370 (1996)). On p. 31, lines 13-18, the Specification describes how polynucleotides encoding TRXP may be used for diagnostic purposes: "The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs." Again, Applicants submit that in the context of this description, the skilled artisan would understand that "an RNA equivalent" in reference to a DNA molecule, is composed of the same linear sequence of nucleotides as the reference DNA molecule with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose. Based at least upon these arguments, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IX. Rejection of Claims 3, 4, 6, 7, 9, 11, and 12 Under 35 U.S.C. §102(b)

Claims 3, 4, 6, 7, 9, 11, and 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kato et al. (WO200005376-A2, February 3, 2000). As stated above (Section V, *infra*), the priority application (Tang 09//107,248) has a priority date of June 30, 1998. The priority application has

substantially the same disclosure as the instant application, and any arguments in rebuttal of the utility rejection in the instant application will also establish the validity of the claim to priority. Therefore, Applicants find no need to substantively address the prior art rejection until the utility issue has been settled; other than by claiming the priority date of June 30, 1998 as valid, and stating therefore that the Kato et al. reference is not prior art.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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Attachments:

Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132; Exhibits (A) through (H).

References:

1. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999).

2. Deval A. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (August 1997).

3. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999).

4. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).

5. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999).

6. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding.

7. Steven E. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-6078 (1998).

8. Merriam-Webster's Collegiate Dictionary; Merriam-Webster OnLine: http://www.m-w.com.